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What Is the Evidence from Past National Institute of Health and Care Excellence Single-Technology Appraisals Regarding Company Submissions with Base-Case Incremental Cost-Effectiveness Ratios of Less Than £10,000/QALY?

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ABSTRACT

Background: The National Institute for Health and Care Excellence has recently proposed that company submissions with a base-case incremental cost-effectiveness ratio (ICER) of less than £10,000/quality-adjusted life-year (QALY) might be eligible for a "fast-track" appraisal. **Objectives:** To explore outcomes relating to previously conducted single-technology appraisals (STAs) with base-case ICERs of less than £10,000/QALY. **Methods:** All STAs with published guidance from 2009 to 2016 were included; those with company base-case ICERs of less than £10,000/QALY were identified and analyzed. A secondary analysis was also conducted for those with a company base-case ICER of £10,000 to £15,000/QALY. Relevant data were extracted and presented in a narrative and in tables. **Results:** In total, 15% (26 of 171) of STAs included a company submission with a base-case ICER of less than £10,000/QALY. Of these, 73% (19 of 26) were given positive recommendations after the first Appraisal Committee meeting, whereas 27% (7 of 26) were initially given a Minded No before receiving a positive recommendation in the final appraisal determination, albeit with restricted recommendations for three technologies. Five STAs had company base-case ICERs of £10,000 to £15,000/QALY and all received a positive recommendation after the first AC meeting. **Conclusions:** Most previous STAs with a company base-case ICER of £10,000 or even £15,000/QALY received a positive recommendation after the first AC meeting, but a number of them proved more complicated and required detailed appraisal, which influenced the final recommendation. This finding might have implications for the proposed fast-track process of the National Institute for Health and Care Excellence.

Keywords: base-case ICERs, health policy, National Institute for Health and Care Excellence (NICE), single-technology appraisals (STAs).

Introduction

The National Institute for Health and Care Excellence (NICE) single-technology appraisal (STA) process has been in existence since 2005. The process is undertaken for a technology for a single indication; it is outlined in detail in the Guide to the Single Technology Appraisal Process [1] and includes the production of a submission by the company that manufactures the technology. The company's submission (CS) to NICE forms the principal source of evidence for decision making in the STA process. The CS is expected to contain an evaluation of the clinical effectiveness and cost-effectiveness of the technology using decision-analytic approaches outlined in the NICE Guide to the Methods of Technology Appraisal [2]. The CS should also include an incremental cost-effectiveness ratio (ICER), expressed as cost per quality-adjusted life-year (QALY), as the measure of the technology's cost-effectiveness. An independent, academic evidence review group (ERG) is charged with the task of critically appraising the CS to identify strengths, weaknesses, and gaps in the evidence presented. The ERG also undertakes exploratory analyses to explore uncertainties around the company's model and resulting ICERs [3,4]. The ERG report, together with the CS, is considered by one of the four NICE Technology Appraisal Committees (ACs) in their deliberations. The findings of the committee are used to produce the appraisal consultation document (ACD); after further considerations and a consultation period, a final appraisal determination (FAD) is produced that results in NICE guidance. In some cases, only a FAD is produced, without the need for an ACD. Within these documents are listed a company's submitted base-case ICER (or range), the ERG's preferred ICER (or range), the AC's preferred ICERs, as well as the committee's recommendations. On the whole, technologies are recommended for reimbursement if their ICER does not exceed the generally accepted NICE threshold of £20,000 to £30,000/QALY

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[2,5], although there is evidence that this threshold might sometimes be higher, even for technologies that do not satisfy criteria for end-of-life or being "highly specialized" [6,7].

Changes to the NICE STA process have recently been proposed after consultation [8]. One of the proposals, and the focus of this article, is that a new "fast-track" appraisal (FTA) process, a variant of the standard appraisal process, might be applied when a company submits a base-case ICER of less than £10,000/QALY [8]. According to the consultation document, the stated intention behind the proposal appears to be twofold: 1) to reduce the time from a technology's approval by the European Medicines Agency to its being made available in the National Health Service in England and Wales and 2) to reduce resource use by the companies and NICE by conducting an abbreviated technology appraisal process (shorter, less extensive evidence review processes by ERGs and fewer AC meetings) [8]. It is worth noting that a second NICE consultation took place, which also proposed an "accelerated technology appraisal" process. This particular process was intended to fast-track treatments that were "likely to provide similar or greater health benefits at a similar or lower cost than technologies already recommended in technology appraisal guidance for the same indication" [9]. After the consultation this was integrated into the FTA process, but it is not the subject of this article.

This project was designed to explore how many STAs (2009–2016) had an original company base-case ICER of less than £10,000/QALY and how many, after the full appraisal process, were recommended in the first ACD and in the FAD. It also assessed whether and by how much the ICER(s) preferred by the AC and stated in the ACD and in the FAD were different from the original company base-case ICER(s), especially if the ICER exceeded the generally accepted NICE threshold of £20,000 to £30,000/QALY [2,5]. This enabled an evidence-based assessment of the outcomes for previous STAs with company base-case ICERs of less than £10,000/QALY.

The research therefore aimed to answer the following questions:

1. How many STAs had a company submitted base-case ICER of less than £10,000/QALY, or the technology dominated its principal comparator?
2. How many of these technologies received a positive recommendation in the ACD (or in the FAD, in those cases without an ACD)?
3. How many of these technologies received a "No" or "Minded No" in the ACD?
4. What reasons were given in the ACD for not recommending the technology?
5. What was the final ICER and recommendation in the FAD?

A secondary analysis was also conducted on STAs with an original company base-case ICER of between £10,000 and £15,000/QALY to determine whether outcomes were any different for this group.

Methods

A content analysis was undertaken of documents relating to all STAs conducted by NICE between 2009 and December 2016 by members of research teams from the University of Sheffield and the University of Liverpool. This study focuses on 2009 onward because the STA process, after 4 years of development, had become largely standardized by this point [10]. A first screen was conducted to identify those STAs with a company base-case ICER of less than £10,000/QALY, as reported in the first ACD (or FAD if there was no ACD). More extensive data were then extracted into a standard form from the ACD and FAD documents relating to these STAs. The data to be extracted included the following: technology appraisal (TA) number, title of STA, date of FAD, name of company, ERG, disease area, company base-case ICERs, AC-preferred ICERs in the ACD, ACD recommendation (and details), AC-preferred ICERs in the FAD, and the FAD recommendation (and details).

Data from the first 100 STAs with FADs had been collected for a previous project, which covered STAs from March 2009 to March 2014 [3,4,6]. These data were extracted and checked by the two reviewers from the Sheffield team and, in some instances, checked also by a member of the Liverpool team. When necessary, the original documents were all rechecked. The relevant documents of STAs from April 1, 2014, to December 2016 were publicly available on the NICE Web site and were checked and extracted by one member of the Liverpool team and double-checked by a second member. All ambiguous data were checked and discussed with all other members of the project team. The principal findings are summarized in a narrative and presented in tables, when relevant. Any instances in which a technology was not recommended wholly in line with the original submission are discussed in detail, as are the issues that became apparent when examining these data.

Results

Between September 2009 and December 2016, there were 171 STAs for which final guidance had been published. These did not include STAs that had been withdrawn or for which the process had started but had been suspended. Nor did it include STAs in which the relevant ICERs were commercial-in-confidence (e.g., TA410), in which all the necessary documents are not available online (e.g., TA368, TA372, TA376, and TA396) or in which no company base-case ICER was reported (a cost-minimization analysis) (e.g., TA191). Such STAs were therefore excluded from this analysis because the ICERs were absent or unusable. The final total was 171 STAs, for which final guidance had been published. Out of these 171 STAs, 117 were excluded because none of the company base-case ICERs reported in the ACD or FAD was £10,000/QALY or less (or dominated the principal comparators). Nevertheless, five of these STAs had company base-case ICERs between £10,000 and £15,000/QALY (TA216, TA275, TA345, TA355, and TA400). These were considered a potential group of interest, and so are considered separately later. Out of the remaining 54 STAs, 28 had multiple company base-case ICERs for the principal indication (because of the provision of ICERs for different scenarios, comparisons, and subgroups), one or more of which was less than £10,000/QALY *and* one or more of which was more than £10,000/QALY. These were excluded from the primary analysis because they were unlikely to be fast-tracked given the presence of ICERs of more than £10,000/QALY for certain relevant subgroups or comparisons. These STAs are also considered in more detail later. The total number of STAs with company base-case ICERs that all either dominated current treatments or were less than £10,000/QALY in all comparisons was 26, which represents 15% (26 of 171) of all STAs with usable ICERs and published guidance. This is consistent with the 15% figure quoted by NICE [8]. A flowchart of the selection process is shown in Figure 1. F1

STAs with All Company Base-Case ICERs of Less Than £10,000/QALY or Dominating Comparators

The technologies in 19 of these 26 STAs (73%) received a positive recommendation after the first AC meeting. In 13 of these 19 STAs (68%) only a FAD was issued; there was no ACD (see Table 1). In 8 of these 13 STAs (62%), the companies' base-case ICERs (or conclusion on dominance), as recorded in the T1

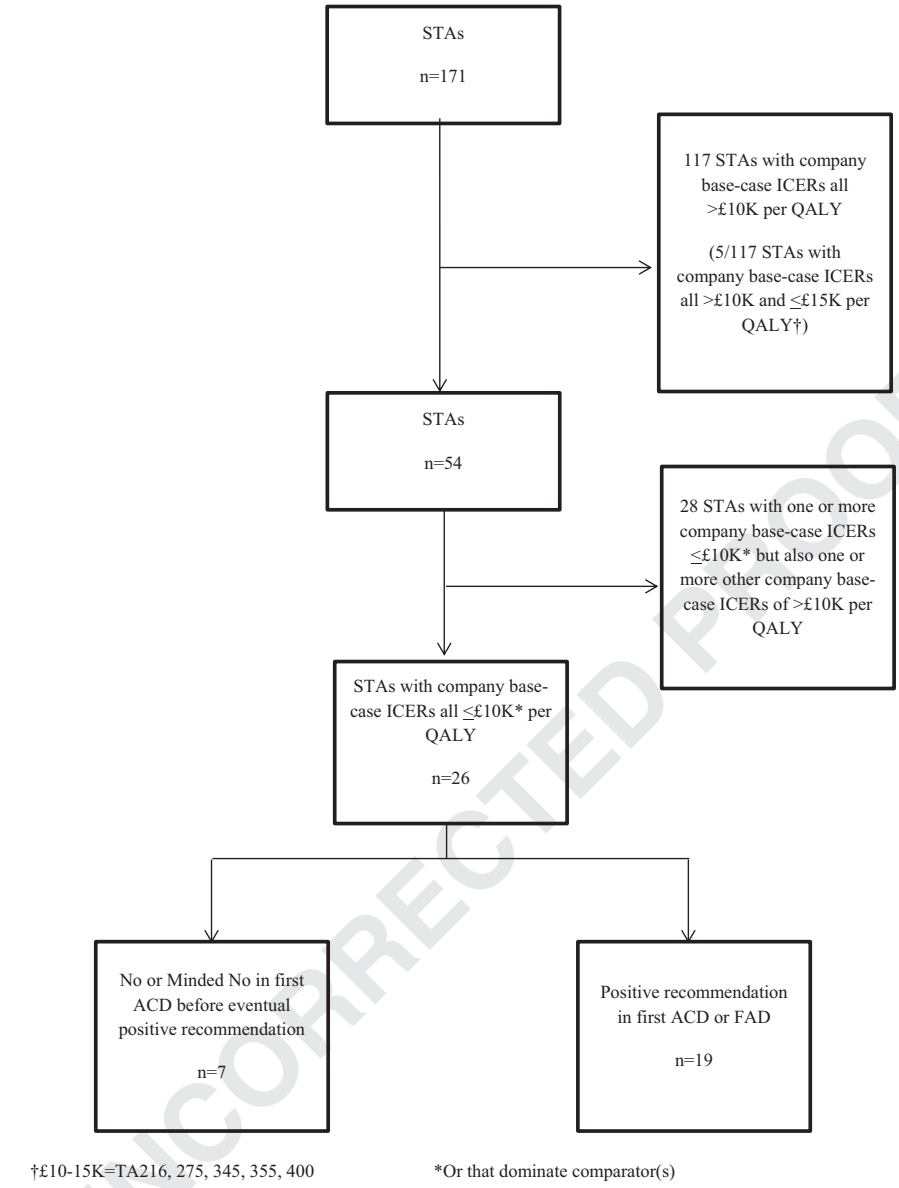

Fig. 1 – PRISMA flowchart of STA selection process. ACD, appraisal consultation document; FAD, final appraisal determination; ICER, incremental cost-effectiveness ratio; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; QALY, quality-adjusted life-year; STA, single-technology appraisal.

committee documents, remained the preferred ICER of the committee (including technologies with a patient access scheme [PAS] in the case of TA305). In the other five STAs, the AC-preferred ICER in the FAD was not explicitly stated (because of a PAS in the case of TA294) in three cases and was higher in two cases, but each technology was stated to be cost-effective. For 6 of the 19 technologies that generated positive recommendations, first in an ACD and then later in the FAD, the AC-preferred ICER in the FAD was the same as the company's base-case ICER in one STA and higher than the company's base-case ICER in five STAs (but still <£10,000/QALY in four STAs). In one STA (TA335), the AC-preferred ICER in the FAD, and its relationship to the company base-case ICER, was unclear. The details of these 19 STAs are presented in Table 1.

Seven of the 26 STAs with all company base-case ICERs of less than £10,000/QALY received a Minded No in the first ACD. All these technologies ultimately received a positive recommendation in the FAD, but in some cases this recommendation was restricted by subgroup. The details of these seven STAs are presented in Table 2. In each case, the AC considered that the analyses provided by both the company and the ERG were inadequate for making a decision, and the AC could not identify a plausible ICER per QALY on the basis of the evidence and model as presented.

Four of the seven technologies were recommended fully in the FAD. Nevertheless, it should be noted that despite all four of these technologies originally dominating comparators or having company ICERs of less than £10,000/QALY, almost all the final ICERs preferred by the AC and stated in the FADs fell between £10,000 and £30,000/QALY, on the basis of the additional analyses requested by the AC and conducted by the company or ERG.

The remaining three of these seven STAs had more restrictive recommendations in the FAD. Two involved treatments for mental health conditions: aripiprazole for adolescent

Table 1 – Summary of STAs with company base-case ICERs <£10,000/QALY that received a positive recommendation at first time of asking.

TA number	FAD date	Technology	Disease area	ERG	ACD, FAD	FAD-preferred ICER	Relative to original ICER
230	2011	Bivalirudin	Cardiovascular	ScHARR	FAD	Dominates	Same*
236	2011	Ticagrelor	Cardiovascular	LRiG	ACD, FAD	<£10,000	Higher
264	2012	Alteplase	Cardiovascular	ScHARR	FAD	<£10,000	Same†
267	2012	Ivabradine	Cardiovascular	BMJ Evidence	ACD, FAD	<£10,000	Same
290	2013	Mirabegron	Urogenital	BMJ Evidence	ACD, FAD	<£10,000	Higher
292	2013	Aripiprazole	Mental health	ScHARR	FAD	Dominates	Unclear
294	2013	Aflibercept	Eye	Aberdeen	FAD	Dominates (with PAS)	Same†
298	2013	Ranibizumab	Eye	Aberdeen	FAD	Dominates	Same
305	2014	Aflibercept	Eye	Warwick	FAD	<£10,000 and dominates (with PAS)	Same
318	2014	Lubiprostone	Digestive system	York CRD	FAD	Dominates	Same
325	2014	Nalmefene	Alcohol dependence	ScHARR	ACD, FAD	<£10,000	Higher
327	2014	Dabigatran etexilate	Cardiovascular	BMJ	FAD	Unclear but within acceptable range	Higher
335	2015	Rivaroxaban	Cardiovascular	ScHARR	ACD, FAD	Unclear but within acceptable range	Unclear
346	2015	Aflibercept	Eye	Aberdeen	ACD, FAD	Unclear but within acceptable range (with PAS)‡	Higher
350	2015	Secukinumab	Psoriasis	Aberdeen	FAD	Unclear but within acceptable range (with PAS)	Unclear
366	2015	Pembrolizumab	Cancer	LRiG	FAD	Unclear but within acceptable range (with PAS)‡	Unclear
407	2016	Secukinumab	Musculoskeletal	Kleijnen SR	FAD	<£10,000 (with PAS)	Same
408	2016	Pegaspargase	Blood and immune	Kleijnen SR	FAD	Dominates	Same
418	2016	Dapagliflozin	Diabetes	Warwick	FAD	Unclear but within acceptable range	Higher

Q5 ACD, appraisal consultation document; CRD; ERG, evidence review group; FAD, final appraisal determination; ICER, incremental cost-effectiveness ratio; LRiG; PAS, patient access scheme; QALY, quality-adjusted life-year; ScHARR, School of Health and Related Research; STA, single-technology appraisal; TA, technology appraisal.

* Different figures, but still dominates.

† A specific final ICER was confidential or not reported.

‡ Includes PAS for comparators.

Table 2 – Summary of STAs with company base-case ICERs <£10,000/QALY that received an initial Minded No recommendation in the ACD.

TA number	FAD date	Technology	Disease area	ERG	ACD reason for decision	FAD decision	FAD ICER (source)
213	2011	Aripiprazole	Mental health	Southampton	4.7, 4.12: The AC requested more evidence on comparisons other than olanzapine, especially for risperidone, the principal, routinely used comparator in UK clinical practice. 4.14: The AC was concerned that, because of a number of uncertainties in the model, the ICER could be as high as £233,000/QALY gained (in line with sensitivity analyses conducted by the ERG) and that aripiprazole was dominated by risperidone in the ERG's exploratory analyses.	1.1: Recommended only in a subgroup of the original indication (people aged 15–17 y who are intolerant of risperidone, or for whom risperidone is contraindicated, or whose schizophrenia has not been adequately controlled with risperidone)	4.12: As first line, the ICERs ranged from £52,750 to £108,800 when compared with treatment sequences in which risperidone is used first (company's updated base-case analysis)
229	2011	Dexamethasone implants	Eye	Aberdeen	4.35: Submission did not compare the new technology with any of the active comparators listed in the scope and identified by the ERG along with other stakeholders. Cost of treatment and extrapolations beyond data from the trial "were not plausible and did not reflect clinical practice in the UK." The committee was therefore unable to estimate the most plausible ICER.	1.1: Recommended	4.20: £26,300 (company's updated base-case analysis)
260	2012	Botulinum toxin type A	Chronic migraine	Warwick	4.19: On the basis of the evidence submitted to the AC, it was unable to conclude whether botulinum toxin type A was cost-effective compared with standard care. The central estimate of probabilistic ICER was not presented and there was uncertainty in many of the modeled parameters.	1.1: Recommended	4.15: £18,900 (ERG analysis of company's updated base-case analysis)
261	2012	Rivaroxaban	Blood and immune	ScHARR	1.2, 4.13, 4.15, 4.16: The main limitation of the model from the AC's point of view was that patients were treated with the drug only for 12 mo, yet in practice people may need ongoing anticoagulation. The AC also considered the assessment of cost-effectiveness in different subgroups to be uncertain and therefore requested further evidence to support the assumptions.	1.1: Recommended	4.13, 4.16: Most likely ICERs based on length of treatment duration ranged from dominating comparators (3 mo) to £19,400/QALY for people who need treatment beyond 12 mo (ERG analysis)

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Table 2 – *continued*

TA number	FAD date	Technology	Disease area	ERG	ACD reason for decision	FAD decision	FAD ICER (source)
308	2014	Rituximab	Blood and immune	ScHARR	4.17: The AC concluded that none of the ICERs presented by the manufacturer and the ERG provided an accurate cost-effectiveness estimate because of uncertainties pertaining to model parameters, such as unrealistic outpatient costs and utility values and incomplete and inappropriate treatment sequences. Additional analyses were needed.	1.1: Recommended only if further cyclophosphamide treatment would exceed the maximum cumulative cyclophosphamide dose; or cyclophosphamide is contraindicated or not tolerated; or the person has not completed their family, and treatment with cyclophosphamide may materially affect their fertility; or the disease has remained active or pro[illegible]ed despite a course of cy[illegible]osphamide lasting 3–6 mo; or the person has had uroepithelial malignancy	4.18: £12,100 for people who can have cyclophosphamide; < £30,000 for those who cannot (ERG analysis)
312	2014	Alemtuzumab	Central nervous system	Southampton	4.10, 4.11: The AC concluded that the primary outcome measure for the MTC should be sustained accumulation of disability lasting 6 mo because this was a coprimary outcome in the clinical trials. The number of QALYs accumulated over the lifetime of the model was deemed to be implausibly low.	1.1: Recommended	4.21: ICER considered to be between £13,600 and £24,500 compared with glatiramer acetate and £8,900 (4.22) compared with fingolimod for a different population (company's updated base-case analysis)
367	2015	Vortioxetine	Mental health	York CRD	1.2, 4.12, 4.20: The only population modeled was for second-line treatment; AC was interested in other comparisons/lines. 4.12, 4.13, 4.16: The AC thought that the model structure lacked validity and that the resource use and costs did not reflect the pathway of care for the indicated population.	1.1: Recommended only in those people who have had an inadequate response to two antidepressants within the current episode (third line)	4.12: All scenario ICERs against all comparators were <£9,000 when equal efficacy between treatments is assumed (company's updated base-case analysis)

Q6 AC, Appraisal Committee; ACD, appraisal consultation document; CRD; ERG, evidence review group; FAD, final appraisal determination; ICER, incremental cost-effectiveness ratio; MTC, mixed treatment comparison; PAS, patient access scheme; QALY, quality-adjusted life-year; ScHARR, School of Health and Related Research; STA, single-technology appraisal; TA, technology appraisal.

schizophrenia (TA213) and vortioxetine for major depressive episodes (TA367). In TA213, aripiprazole was originally indicated in the CS as a first-line therapy for the treatment of schizophrenia in adolescents (aged 15–17 years) and the company base-case ICER was reported as £6200/QALY compared with olanzapine. Nevertheless, the AC considered the principal comparator to be risperidone; ERG analyses had reported much higher ICERs for this comparison. Given that the final ICERs for aripiprazole as a first-line therapy were in excess of £30,000/QALY, the final recommendation restricted its use to first-line therapy only for patients who were intolerant to, or contraindicated for, the principal treatment, risperidone. In a similar way, the CS in TA367 had restricted vortioxetine to second-line treatment, but the FAD recommendation restricted reimbursement to third-line treatment, that is, for patients who had had an inadequate response to two antidepressants within the current episode. Once more, the initial Minded No recommendation was due in part to the AC stating that relevant comparisons were absent from the CS. The third STA with restricted recommendations was for rituximab for antineutrophil cytoplasmic antibody–associated vasculitis (TA308). The initial Minded No was because the AC was uncomfortable with uncertainties in the models submitted by the company and supplemented by the ERG and therefore requested further analyses. As a result of these analyses, and contrary to the CS, the FAD recommended only rituximab for treatment-naive patients in certain circumstances.

Overall, the principal reasons for the Minded No recommendations in these seven STAs, despite their low ICERs, might be summarized as follows (a single submission might be affected by a number of issues): implausible results or ICERs due to the models' failure to reflect clinical practice (TA229, TA261, and TA367) or uncertainties in the model parameters or assumptions (TA213, TA260, TA261, TA308, and TA367). The need for additional analyses was also precipitated by a failure of the models to take into account or use the comparisons (TA213, TA229, and TA367) or outcomes (TA312) that the ACs deemed most relevant.

STAs with Company Base-Case ICERs of £10,000 to £15,000/QALY

Given that the proposed figure of £10,000/QALY for NICE fast-track consideration is not an absolute, we present here the evidence from five further STAs from our sample in which all the company base-case ICERs were less than £15,000/QALY. That is, if one of the criteria for FTA was to be set at £15,000/QALY, then an additional five STAs become relevant to our analysis; thus, in total, 31 of 171(18%) previously completed STAs would be potentially eligible. These five additional STAs are presented in Table 3.

As with most of the STAs with all company base-case ICERs of less than £10,000/QALY that did not receive a Minded No in the ACD, all five of these STAs received a positive recommendation in the first AC meeting (only a FAD was produced, and there was no ACD). In three cases, the AC-preferred ICER in the FAD (the result of ERG analyses in each case) was higher than the original company base-case ICER, but all were less than a cost-effectiveness threshold of £30,000/QALY. Unlike the STAs considered in Table 1, this group includes two cancer technologies: bendamustine for chronic lymphocytic leukemia (TA216) and nivolumab for advanced melanoma (TA400).

STAs with Company Base-Case ICERs Ranging from Less Than £10,000/QALY to More Than £10,000/QALY

In total, 28 of 171 (16%) relevant STAs in this sample had one or more company base-case ICERs of less than £10,000/QALY as well as one or more ICERs of more than £10,000/QALY (see Table 4). These were evenly spread across disease areas and ERGs, but it is noticeable that the last 2 years had more such STAs than the previous 6 years (15 for 2015–2016 compared with 13 for 2009–2014). This perhaps reflects the increasing complexity of the assessments being conducted in the NICE STA process.

It is no surprise that the picture for these 28 STAs is far more fragmentary than for those 26 STAs with all the company base-ICERs less than £10,000/QALY. Only 39% (13 of 28) received an unrestricted, positive recommendation at the first AC. In seven of these, no ACD was produced at all (only a FAD was produced), that is, 25% (7 of 28) compared with 50% (13 of 26) in the group with company base-ICERs all less than £15,000/QALY. Furthermore, technologies received a No or Minded No for all groups in 25% (7 of 28) of these STAs after the first AC and others were recommended in specific subgroups or circumstances only in 29% (8 of 28). All the technologies in these 28 STAs ultimately received a positive recommendation in the FAD, but in 32% (9 of 28) the recommendation was restricted to certain subgroups or lines of treatment and, in seven cases, it was conditional on a PAS. In five of these seven cases, the PAS had been submitted along with the original CS (see Table 4).

Discussion

Twenty-six STAs in this sample would have satisfied the basic criterion for the proposed NICE FTA process; that is, all of a company's submitted base-case ICERs for a technology and indication were less than £10,000/QALY. Following the example of previous STAs, this approach would make up to 18% of future STAs eligible for such an FTA process. Our analysis found that 73% (19 of 26) of these STAs received a straightforward, positive

Table 3 – Summary of STAs with company base-case ICERs of £10,000–£15,000/QALY.

TA number	FAD date	Technology	Disease area	ERG	ACD, FAD	FAD-preferred ICER	Relative to original ICER
216	2011	Bendamustine	Cancer	PENTAG	FAD	<£10,000	Lower (£12,000)
275	2013	Apixaban	Cardiovascular	BMJ Evidence	FAD	<£20,000	Higher
345	2015	Naloxegol	Digestive system	Kleijnen SR	FAD	<£13,000	Same
355	2015	Edoxaban	Cardiovascular	LRiG	FAD	<£16,000	Higher
400	2016	Nivolumab	Cancer	BMJ Evidence	FAD	<£30,000* (with PAS)	Higher

ACD, appraisal consultation document; ERG, evidence review group; FAD, final appraisal determination; ICER, incremental cost-effectiveness ratio; LRiG; PAS, patient access scheme; QALY, quality-adjusted life-year; STA, single-technology appraisal; TA, technology appraisal.

* As long as combination technology is costed according to its PAS.

Table 4 – Summary of STAs with company base-case ICERs ranging from less than to more than £10,000/QALY.

TA number	FAD date	Technology	Disease area	ERG	ACD decision	FAD decision
182	2009	Prasugrel	Cardiovascular	LRiG	Recommended	Recommended
186	2010	Certolizumab pegol	Musculoskeletal	West Midlands	Minded No	Recommended (with PAS*)
197	2010	Dronedarone	Cardiovascular	York CRD	Not recommended	Recommended for second-line treatment only
203	2010	Liraglutide	Blood and immune	Aberdeen	Restricted recommendations	Recommended (in certain subgroups)
248	2012	Exenatide	Blood and immune	Warwick	Recommended	Recommended
249	2012	Dabigatran etexilate	Cardiovascular	York CRD	Minded No	Recommended
252	2012	Telaprevir	Hepatitis	Southampton	No ACD	Recommended
253	2012	Boceprevir	Hepatitis	Southampton	No ACD	Recommended
287	2013	Rivaroxaban	Blood and immune	Southampton	No ACD	Recommended
293	2013	Eltrombopag	Blood and immune	Aberdeen	Recommended	Recommended
315	2014	Canagliflozin	Endocrine	Southampton	Restricted recommendations	Recommended (in certain subgroups)
317	2014	Prasugrel	Cardiovascular	LRiG	Recommended	Recommended
326	2014	Imatinib	Cancer	Southampton	Recommended	Recommended
330	2015	Sofosbuvir	Hepatitis	Southampton	Minded No	Recommended
331	2015	Simeprevir	Hepatitis	Southampton	Restricted recommendations	Recommended
336	2015	Empagliflozin	Endocrine	Warwick	Minded No	Recommended (in certain subgroups)
341	2015	Apixaban	Cardiovascular	LRiG	No ACD	Recommended
342	2015	Vedolizumab	Digestive system	ScHARR	Restricted recommendations	Recommended (with PAS*)
349	2015	Dexamethasone implants†	Eyes	BMJ Evidence	Restricted recommendations	Recommended (in certain subgroups)
354	2015	Edoxaban	Cardiovascular	BMJ Evidence	No ACD	Recommended
359	2015	Idelalisib	Cancer	Warwick	Minded No and No	Recommended (in certain subgroups) (with PAS*)
363	2015	Ledipasvir/sofosbuvir	Hepatitis	ScHARR	Restricted recommendations	Recommended (in certain subgroups) (with PAS)
364	2015	Daclatasvir	Hepatitis	York CRD	Restricted recommendations	Recommended (in certain subgroups) (with PAS)
365	2015	Ombitasvir/paritaprevir/ritonavir ± dasabuvir	Hepatitis	Southampton	Recommended	Recommended
384	2016	Nivolumab†	Cancer	Southampton	No ACD	Recommended
413	2016	Elbasvir-grazoprevir	Hepatitis	Kleijnen SR	No ACD	Recommended (with PAS*)
415	2016	Certolizumab pegol	Musculoskeletal	ScHARR	Restricted recommendations	Recommended (in certain subgroups) (with PAS*)
424	2016	Pertuzumab	Cancer	ScHARR	Not recommended	Recommended

ACD, appraisal consultation document; CRD; ERG, evidence review group; FAD, final appraisal determination; ICER, incremental cost-effectiveness ratio; LRiG; PAS, patient access scheme; QALY, quality-adjusted life-year; ScHARR, School of Health and Related Research; STA, single-technology appraisal; TA, technology appraisal.

* PAS submitted with original company submission.

† Includes PAS for comparators.

recommendation with an AC-preferred ICER in the FAD that fell below the £30,000/QALY threshold of cost-effectiveness generally applied by NICE [2,5].

Nevertheless, the seven STAs with company base-case ICERs of less than £10,000/QALY that received a Minded No in the ACD give particular pause for thought when considering the implications of these findings for the proposed FTA process. In four of these STAs, the AC-preferred ICERs in the FAD, as a result of additional analyses performed by the company or the ERGs, had risen to almost £30,000/QALY (still within existing thresholds of cost-effectiveness). Yet in the other three STAs (TA213, TA308, and TA367) the result was a recommendation restricted to certain subgroups or lines of treatment. In the case of TA213, the final preferred ICERs for the original proposal of first-line treatment were well in excess of the £30,000/QALY threshold. The National Health Service could therefore have ended up paying for a treatment for certain patients that might normally have been designated as "not cost-effective," with the obvious implications and opportunity costs [5,11,12]. It might be the case that the health system would be willing to fund non–cost-effective treatments for certain subgroups in return for providing more timely access to new treatments and a faster, less expensive TA process [8], although some might disagree [12].

The NICE proposal has stated that criteria for inclusion in the FTA process would be "the availability of strong evidence (with a low degree of decision uncertainty)" and that the ICER is indeed likely to be less than £10,000/QALY. It was also anticipated that such technologies would be identified by NICE "following an analysis of the company's submission, supported by external review" [8]. It is possible that STAs with issues, such as the seven STAs with a company base-case ICER of less than £10,000/QALY, and which received a Minded No in the ACD, might have been identified by this process and "re-routed" to the standard STA process. After all, the CS and models in four of these seven STAs were potentially easily identifiable as having a high degree of decision uncertainty on account of their failure to provide comparisons against the most relevant current treatments (TA213, TA229, and TA367) and/or their failure to reflect UK clinical practice (TA229, TA261, and TA367). It is, however, questionable whether a more limited appraisal process might have identified the uncertainties in the model parameters and assumptions that affected five of these STAs (TA213, TA260, TA261, TA308, and TA367). Indeed, the current process's heavy reliance on the ERGs to identify such issues is well known [3].

On the basis of the evidence, the group of 26 STAs with ICERs less than £10,000/QALY, and the group of five STAs with ICERs between £10,000 and £15,000/QALY, all do appear to represent a generally quite homogeneous type of STA. Only 13 of these 31 STAs had multiple ICERs and, of course, the range was very narrow (from the new technology dominating comparators to always being <£15,000/QALY). This means that 18 of these 31 STAs (58%) had only a single company base-case ICER. The groups and scenarios within these appraisals were fairly homogeneous and thus required a less complex methodology than did other STAs. This accords with the NICE consultation proposal that "the weight and complexity" of the appraisals should be "in proportion to the technical challenges and the risks posed by the evidence that it considers" [8]. And thus, the FTA process was only to be for "the appraisal of health technologies for which a confident judgement about value for money can be made at an early stage" [8]. Nevertheless, such a judgment could not possibly be made, for example, for the 28 STAs with company base-case ICERs both less than and more than £10,000/QALY, in which companies submitted multiple base-case ICERs for their technology, which might range from dominating to being dominated by comparators (e.g., TA349) on account of different subgroups, treatment lines, or scenarios. Such technologies must be appraised via the standard process.

Another scenario arises when a relevant comparator product already has a confidential PAS in place with the Department of Health. In this case, an ERG is required to generate results taking into account all the PAS discounts. In our data set, two of the STAs (TA346 and TA366) with company base-case ICERs of less than £10,000/QALY were subject to this additional process, as were two STAs (TA384 and TA415) within the group containing multiple ICERs, some of which were less than £10,000/QALY. This information can be identified at the outset and would allow some technologies to be quickly categorized as not being eligible for the FTA process, if the presence of such an issue was deemed to require more work.

One particular pattern is noticeable in the 19 STAs with all ICERs less than £10,000/QALY and with straightforward positive recommendations. Six of the 19 (32%) comprise treatments for cardiovascular disease and 4 (21%) relate to treatments for eyes. We consider that these disease areas are disproportionately highly represented in this group. In a study of the first 100 STAs with published guidance (2009–2014), frequencies were 11% for cardiovascular disease therapies and 7% for eye therapies and treatments for cancer; for blood and immune system and musculoskeletal conditions, frequencies were all higher than 7% [4,6,10]. In our data set, three of the four "eye" STAs evaluated aflibercept for different indications and this drug has a relatively low-intensity regimen (with relatively low associated costs) compared with currently licensed comparators [13], for example, ranibizumab, which was the subject of the fourth "eye" STA. The relatively higher proportions of cardiovascular and eye treatments in this sample of STAs might also be due in part to the lower costs of treatments for these particular disease areas relative to others, such as cancer or musculoskeletal conditions [14,15]. There did not appear to be any particularly noticeable increase in these STAs over time (see Tables 1 and 2): there were the same number of STAs (n = 4) with a company base-case ICER of less than £10,000/QALY in 2011, 2012, and 2013, and only slight increases in 2014 (n = 6) and 2015 (n = 5). This might, however, change in the future.

In 74% (23 of 31) of STAs with technologies with company base-case ICERs all less than £15,000/QALY, this represented the first time the technology was being assessed by NICE (for any indication). These cases therefore all potentially represented cost precedents for future submissions, even for different indications. In five of the remaining eight STAs (TA264, TA275, TA292, TA327, and TA335), the technologies had received previous recommendations for essentially the same indication, either as long as 5 years before the relevant appraisal, for example, alteplase for acute ischemic stroke in 2007 (TA122) and 2012 (TA264), or as little as 1 year before the relevant appraisal, for example, apixaban for embolisms in 2012 (TA245) and 2013 (TA275). In only three cases were there previous appraisals of the same technology for different indications: bendamustine for treating chronic lymphocytic leukemia in 2011 (TA216) had been preceded by bendamustine for non-Hodgkin lymphoma in 2010 (TA206); rituximab for treating antineutrophil cytoplasmic antibody–associated vasculitis in 2014 (TA308) had been preceded by TAs for a number of lymphoma indications and rheumatoid arthritis between 2002 (TA37) and 2009 (TA174); and finally ranibizumab for treating choroidal neovascularization associated with pathological myopia in 2013 (TA298) had been the subject of previous appraisals between 2008 and 2011 for macular degeneration and macular edema (TA155, TA229, and TA237).

The strength of this research is that it represents an analysis of all NICE STAs with published final guidance from September 2009 to December 2016, and thus offers an excellent summary of current and recent practice. The double-checking of all key data

across the 171 included STAs, by at least two experienced health technology assessment researchers from two research teams (Sheffield and Liverpool), reduced the likelihood of inconsistency and inaccuracy in the data. In addition, the method of analysis was descriptive, which reduces the likelihood of overstating relationships in the data, and an inclusive approach was taken to managing data that were not straightforward, for example, the presence of multiple ICERs.

There are, however, limitations to this study. There are inherent weaknesses in using documentary analysis in that the researcher is able to analyze only what has been reported. The level and type of detail provided in and across the ACDs and FADs could be very different, which made data extraction at times a matter of interpretation. The so-called original company base-case ICERs, as reported in the ACD or FAD, are possibly likely to be different in an unknown number of instances from the ICERs submitted by companies at the very start of the process. This is because, as a minimum, they will have been subject to the clarification process led by the ERG [1], and so could have already been revised before the first AC meeting and the committee's request for any revisions or additional analyses. It is also unclear exactly how a new FTA process might be operationalized, and so assumptions have had to be made in this study and it is not possible to know exactly how far such a process might or might not identify STAs with issues requiring more extensive work. Finally, it is not possible to determine from the present study and analysis whether the proposed FTA process will be adequate to identify all the issues that might arise with a submission that has a company base-case ICER of less than £10,000/QALY or how far the existence of this criterion might influence submissions; this study explored only what had happened with previous STAs that satisfied this basic criterion. These limitations suggest that caution should be exercised regarding some of the conclusions drawn from the evidence.

Conclusions

Most of the previous STAs with a company base-case ICER of £10,000 or even £15,000/QALY received a positive recommendation after the first AC, but a number proved more complicated and required detailed appraisal, which influenced the final recommendation. In 19 of the 26 STAs that satisfy the £10,000/QALY threshold in this sample, the technologies received a positive recommendation after the first AC meeting with little or no amendment to the original company base-case ICERs in the FAD. The same finding applied to another group of five STAs with company base-case ICERs of less than £15,000/QALY. Nevertheless, in seven of the STAs with company base-case ICERs less than £10,000/QALY, the technology received an initial Minded No and, in three cases (43%), the indicated patient groups were more restricted in the final recommendation than in the companies' original submissions. Additional analyses and work by the companies and ERGs had demonstrated that the relevant base-case ICERs might actually be much higher and the technologies might not be cost-effective for certain patient groups. It is uncertain whether an FTA process would have identified these issues.

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Supplemental Materials

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